REMARKS/ARGUMENTS

The Invention

The present invention is directed to methods of treating a tumor in a mammal involving delivering to the tumor a serum-stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion. Delivery of the nucleic acid-lipid particle is by injection at a site distal to the tumor in the mammal. The lipid portion of the nucleic acid-lipid particle comprises a cationic lipid, a neutral lipid, a lipid conjugate that prevents aggregation during formulation. In some embodiments, a prodrug is also administered to the mammal. In other embodiments, a chemotherapeutic agent is also administered to the mammal. In some embodiments, delivery of the nucleic acid-lipid particle is intravenous.

Status of the Claims

Applicants wish to thank Examiners McGarry and Zara for extending the courtesy of the interview held on June 11, 2003 with Applicants' representatives Dr. Mark Murray, Eugenia Garrett-Wackowski, and Carol Fang. During this interview, a number of issues were clarified which have helped Applicants to more fully address the concerns of the Examiners. Applicants thank Examiners McGarry and Zara for her time.

After entry of this amendment, claims 1-12, 14-35, 37-41, and 43-61 are pending. Claims 13, 36, and 42 have been canceled without prejudice to future prosecution. Support for these amendments is found throughout the specification and claims as originally filed. Thus, no new matter is added by these amendments. Claims 1-12, 14-35, 37-41, 43-48, 50, 55-57, and 60-61 have been amended to clarify the scope of the claims. Claims 1-28 and 35-46 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement; claim 6 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description; claims 4, 6, and 7 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite; claims 1-4, 8, 10-12, 16-18, 23, 28, 39-42, 44, and 46 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated. These rejections are addressed below.

Rejections Under 35 U.S.C. §112, first paragraph

The Examiner initially maintained the rejection of claims 1-28 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

As previously explained, a particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without ***undue*** experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. It is important to note that the possibility that some experimentation, even if such experimentation is complex or extensive, may be required for the practice of the invention does not necessarily mean that the invention is not enabled:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See*, MPEP § 2164.01.
>
> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP § 2164.06, citing *In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988).
>
> As MPEP § 2164.02 states, "[a] rigorous or an invariable exact correlation is not required" between a particular model and a specific condition.
>
> As set forth in MPEP § 2164.08, a rejection for undue breadth is inappropriate where "one of skill could readily determine any one of the claimed embodiments."

During the interview, Applicants discussed several aspects of the rejection with the Examiner. For example, it was pointed out to the Examiner that the specification provides (1) teachings regarding therapeutic nucleic acids; (2) teachings regarding preparation and properties of nucleic acid-lipid particles; (3) teachings regarding neoplasias suitable for treatment using the nucleic acid-lipid particles of the present invention; and (4) teachings regarding administration of nucleic acid-lipid particles (*see, e.g.*, page 10, line 14 to page 14, line 24; page 14, line 25 to page 18, line 31; page 19, line 28, to page 20, line 16; and page 21, lines 20 to page

22, lines 27). Moreover, as discussed with the Examiner, the teachings in the specification are affirmed by the Declaration of Dr. Ian MacLachlan, originally submitted on March 8, 2002 in response to the Final Office Action mailed October 10, 2001.

During the interview of June 11, 2003, and in the Office Action mailed October 2, 2002, the Exmainer acknowledged that Applicants have provided numerous examples of *in vitro* and *in vivo* gene delivery to cells and tumors. In addition, the Examiner acknowledged that Applicants have provided numerous examples of successful tumor reduction by administration of nucleic acid-lipid particles using the presently claimed methods. However, the Examiner maintains the rejection that undue experimentation is required to enable treatment of any neoplasia in an animal. Applicants respectfully traverse this rejection.

During the interview and in the accompanying Declaration of Dr. Mark Murray, Applicants presented data unequivocally demonstrating that nucleic acids encapsulated in the lipid portion of the nucleic-acid lipid particles of the present invention are specifically expressed in tumors cells and not in normal tissues (*see, e.g.*, Declaration, ¶ 7). Thus, the nucleic acid-lipid particles described and disclosed in the present application can be used to deliver and express any nucleic acid in tumor cells.

As discussed during the interview and acknowledged by the Examiners, Applicants have demonstrated that distal administration of the nucleic acid-lipid particles of the claimed invention can be used to treat multiple types of tumors with multiple classes of nucleic acids (Declaration of Dr. MacLachlan ¶8 and ¶12, previously filed on March 8, 2002). For example, as discussed during the interview, the specification and declaration of Dr. MacLachlan contain multiple working examples demonstrating effective *in vivo* treatment of diverse neoplasias such as melanoma, sarcoma, fibrosarcoma, and colorectal tumors with multiple classes of nucleic acids encapsulated in the nucleic acid-lipid particles of the claimed invention. Specifically, the additional experiments unequivocally demonstrate that diverse classes of nucleic acids encoding cytokines (*e.g.*, IL-12), tumor suppressor proteins (*e.g.*, apoptin), and bacterial toxins (*e.g.*, *Pseudomonas* exotoxin) encapsulated in the nucleic acid-lipid particles of the invention effectively inhibit growth of diverse neoplasias such as sarcoma and colon carcinoma (*see,* Declaration of Dr. MacLachlan ¶7, ¶8, and ¶12). Applicants also pointed out the

working examples in the specification which showed that growth of melanoma, fibrosarcoma, and colorectal tumors was inhibited by distal administration of nucleic acids encoding the suicide gene HSV-TK encapsulated in the nucleic acid-lipid particles of the present invention (*see*, Declaration of Dr. MacLachlan ¶8). The Examiner agreed that all of these data were persuasive in demonstrating that the claimed methods of administering serum-stable nucleic acid-lipid particles can inhibit tumor growth and are effective for treating tumors.

Applicants further noted during the interview that further *in vivo* experiments demonstrate that nucleic acids delivered using the nucleic acid-lipid particles of the present invention are expressed in neuroblastoma cells, glioblastoma cells, melanoma cells, and fibrosarcoma cells. These experiments are discussed in detail by Dr. Mark Murray in the accompanying Declaration (¶8). The Examiners agreed that the experiments were persuasive in demonstrating that nucleic acids administered by delivering the nucleic acid lipid particles of the present invention are actually expressed in tumor cells.

Applicants also noted during the interview that additional *in vivo* experiments demonstrate that the suicide enzyme HSV-TK is also effective in inhibiting proliferation of neuroblastoma cells and melanoma cells. These experiments are discussed in detail by Dr. Mark Murray in the accompanying Declaration (¶10). The Examiners agreed that the experiments were persuasive in supporting claims directed to methods of treating multiple types of tumors by administering the nucleic acid-lipid particles of the present invention.

Finally, Applicants noted for the Examiners that multiple types of cationic lipids, neutral lipids, and lipids that prevent aggregation during formulation can be used in the lipid portion of the nucleic acid-lipid particles of the present invention. The types of lipids that can be used for nucleic acid-lipid particles in which nucleic acids are fully encapsulated in the lipid portion of the particle are discussed in detail by Dr. Mark Murray in the accompanying Declaration (¶11). The Examiners agreed that additional information regarding lipids useful in the nucleic acid lipid particles would also be persuasive in supporting claims directed to methods of treating multiple types of tumors using nucleic acid-lipid particles wherein the nucleic acid portion is fully encapsulated in the lipid portion as disclosed and claimed in the present invention.

Thus, as discussed in detail above, the specification enables claims directed to methods of treating diverse classes of tumors by administering nucleic acid-lipid particles, with diverse classes of nucleic acids encapsulated therein, including nucleic acids encoding suicide enzymes, cytokines, tumor suppressor proteins, and bacterial toxins. Any nucleic acid encapsulated in the nucleic acid-lipid particles of the present invention will be expressed in tumor cells and not in normal tissues. In addition, one of skill in the art would appreciate that multiple lipid formulations can be used for the lipid portion of the nucleic acid-lipid particles of the present invention. Therefore, a skilled artisan, using the teachings of the specification either alone or together with what is known to those of skill in the art, would be able to practice the invention as claimed, ***without*** undue experimentation.

In view of the foregoing remarks, Applicants assert that claims are fully enabled by the specification as originally filed.

In view of the foregoing, Applicants respectfully request that the enablement rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 102(e)

Claims 1-4, 8, 10-12, 16-18, 23, 28, 42, 44, and 46 were initially rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Kim *et al.* (U.S. Patent No. 6,133,243). Claims 1-4, 8, 10-12, 16-18, 23, 28, 39-42, 44, and 46 are also rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Hung *et al.* (U.S. Patent No. 6,197,754). Each of these rejections is addressed in turn below, in the order raised by the Examiner.

For a rejection of claims under § 102(e) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held:

> [A]nticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be ***no difference*** between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.

Id. at 1010 (emphasis added). Anticipation can be found, therefore, only when a cited reference discloses ***all*** of the elements, features or limitations of the presently claimed invention.

As explained above and during the interview, the present invention relates to methods of treating a neoplasia in a mammal involving administering to the mammal a serum-stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion.

1. Rejection of claim s 1-4, 8, 10-12, 16-18, 23, 28, 42, 44, and 46 under 35 U.S.C. § 102(e) over Kim *et al.*

Kim *et al.* was initially cited as teaching methods of treating neoplasia in a mammal comprising the administration of a serum-stable, nucleic acid-lipid particle comprising a fully encapsulated nucleic acid encoding a therapeutic proto-oncogenic polynucleotide.

Applicants noted for the Examiners that the presently claimed methods comprise administering lipid-nucleic acids particles in which the nucleic acids are *fully encapsulated* within the nucleic acid-lipid particles. Since the nucleic acids of the nucleic acid-lipid particles of the present invention are fully encapsulated, degradation of the nucleic acids by nucleases is greatly reduced. As explained by the Applicants during the interview and by Dr. Murray in the accompanying Declaration (¶ 12), the nucleic acid-lipid particles disclosed in Kim *et al.* are lipoplexes of lipid and nucleic acid, *i.e.*, complexes of lipids with nucleic acids in which the nucleic acids are ***not*** encapsulated. More particularly, Kim *et al.*, describe preparation of nucleic acid-lipid complexes by first preparing cationic liposomes. Only after the liposomes are fully formed are they mixed with nucleic acids to form nucleic acid-lipid complexes (*see, e.g.*, col. 38, line 58 to col. 39, line 30). Thus, in contrast to the presently claimed invention, Kim *et al.* do not teach nucleic acids *fully encapsulated* within lipid-nucleic acid particle. During the interview of June 11, 2003, the Examiners agreed that administration of the lipid and nucleic acid complexes described by Kim *et al.* does not anticipate the presently claimed methods of treating neoplasia by administering lipid-nucleic acids particles in which the nucleic acids are *fully encapsulated* within the nucleic acid-lipid particles.

Thus, Kim *et al.* fail to disclose all of the elements of the claimed invention, *i.e.*, methods of treating neoplasia in a mammal comprising the administration of a serum-stable,

nucleic acid-lipid particle comprising a fully encapsulated nucleic acid and does not anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(e) be withdrawn.

2. Rejection of claims 1-4, 8, 10-12, 16-18, 23, 28, 39-42, 44, and 46 under 35 U.S.C. § 102(e) over Hung *et al.*

Hung *et al.* was initially cited as teaching methods of treating neoplasia in a mammal comprising the administration of a serum-stable, nucleic acid-lipid particle comprising a fully encapsulated nucleic acid encoding a therapeutic proto-oncogenic polynucleotide.

Applicants noted for the Examiners that the presently claimed methods comprise administering lipid-nucleic acids particles in which the nucleic acids are *fully encapsulated* within the nucleic acid-lipid particles. Since the nucleic acids of the nucleic acid-lipid particles of the present invention are fully encapsulated, degradation of the nucleic acids by nucleases is greatly reduced. As explained by the Applicants during the interview and by Dr. Murray in the accompanying Declaration (¶ 12), the nucleic acid-lipid particles disclosed in Hung *et al.* are lipoplexes of lipid and nucleic acid, *i.e.*, complexes of lipids with nucleic acids in which the nucleic acids are ***not*** encapsulated. More particularly, Hung *et al.*, describe preparation of nucleic acid-lipid complexes by first preparing cationic liposomes. Only after the liposomes are fully formed are they mixed with nucleic acids to form nucleic acid-lipid complexes (*see, e.g.*, col. 38, line 58 to col. 39, line 30). Thus, in contrast to the presently claimed invention, Hung *et al.* do not teach nucleic acids *fully encapsulated* within lipid-nucleic acid particle. During the interview of June 11, 2003, the Examiners agreed that administration of the lipid and nucleic acid complexes described by Hung *et al.* does not anticipate the presently claimed methods of treating neoplasia by administering lipid-nucleic acids particles in which the nucleic acids are *fully encapsulated* within the nucleic acid-lipid particles.

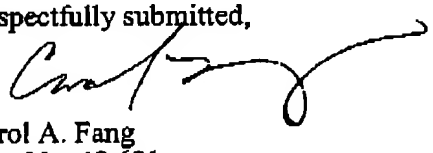
Thus, Hung *et al.* fail to disclose all of the elements of the claimed invention, *i.e.*, methods of treating neoplasia in a mammal comprising the administration of a serum-stable, nucleic acid-lipid particle comprising a fully encapsulated nucleic acid and does not anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(e) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiners believe a telephone conference would expedite prosecution of this application, the Examiners are invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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